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XCVIII.—*Mitragynine and Mitraversine, Two New Alkaloids from Species of Mitragyne.*

By Ellen Field.

The natural order of *Rubiaceæ* is rich in alkaloids, and comprises amongst others the genera *Cinchona*, *Remijia* (yielding Cuprea bark), *Psychotrea* (*Ipecacuanha*), and *Corynanthe* (yielding yohimbine). The present investigation deals with some species of the genus *Mitragyne* of the same order.

A quantity of an alcoholic extract of the leaves of *M. speciosa*, Korth., was supplied by Professor G. Barger, for which he was indebted to Dr. P. P. Laidlaw and the National Medical Research Council. The leaves were obtained from the Malay States and were identified at Kew through the kindness of the Director of the Royal Gardens. This tree has also been recorded from Borneo, the Philippine Islands, and New Guinea. The leaves have now been found to contain an alkaloid, $C_{22}H_{31}O_5N$, for which the name *mitragynine* is suggested.

Alkaloids have been stated to be present in two other species of *Mitragyne.* The bark of *M. africana*, Korth. (Écorce de Xosse), is used in Senegal as a febrifuge, and is believed to contain an alkaloid (Wehmer, "Die Pflanzenstoffe," 1911, p. 728, according to Dragendorff, "Die Heilpflanzen," 1898). Hooper (*Pharm. J.*, 1907, **78**, 453) isolated a crystalline alkaloid from the leaves of *M. parvifolia*, Korth., in a yield of 0·15 per cent. I was unable to obtain any alkaloid from a small specimen of the leaves of *M. parvifolia* at my disposal, but found, on the other hand, a crystalline alkaloid in the leaves of *M. diversifolia*, Hook. f., kindly sent to Professor Barger by Mr. E. D. Merrill, formerly botanist in the Bureau of Science, Manila. For this alkaloid the name *mitraversine* is suggested.

According to Redley (quoted by Hooper, *loc. cit.*) *Mitragyne speciosa* is used in Perak against the opium habit, whilst, according to Dr. P. P. Laidlaw, mitragynine is a local anæsthetic, which finding is of interest, since the alkaloid contains an ester grouping. Its formula may apparently be resolved to $C_{17}H_{22}N(OMe)(CO_2Me)_2$, and it is probably an indole derivative.

EXPERIMENTAL.

Mitragynine, $C_{22}H_{31}O_5N$, *from* M. speciosa.

Preliminary experiments had shown that the salts of the alkaloid with strong mineral acids were apt to form gels and to be precipitated from aqueous solution by excess of the acid. Therefore the residue left by evaporating the alcoholic extract of the leaves was dissolved in glacial acetic acid, and by addition of water a large quantity of resin and chlorophyll was precipitated. In some experiments, the filtrate was purified by means of lead acetate. On making the solution alkaline with ammonia, an amorphous precipitate separated. Ten grams of this (from 2 kilos. of leaves) were dissolved in 75 c.c. of 20 per cent. acetic acid and a hot solution of 6 grams of picric acid in 300 c.c. of water added. The yield of crude picrate was 15 grams. It was crystallised from 100 c.c. of boiling glacial acetic acid, yielding 6 grams of crystals. The yield of the pure picrate is thus 0·3 per cent. of the weight of the leaves, corresponding with 0·2 per cent. of pure base; the content is doubtless higher, and other alkaloids appear to be present, as the amount of viscid base obtained in several experiments was 0·5 per cent.

Mitragynine picrate, $C_{22}H_{31}O_5N,C_6H_3O_7N_3$, is the only salt suitable for the initial purification of the alkaloid. It forms orange-red, slender needles from methyl alcohol, and melts at 223—224° (Found: C=54·2, 54·3; H=5·5, 5·6; N=9·4; picric acid [by nitron]=35·3. $C_{22}H_{31}O_5N,C_6H_3O_7N_3$ requires C=54·3; H=5·5; N=9·1; picric acid=37·2 per cent.). The free *alkaloid* was obtained by dissolving the picrate in boiling glacial acetic acid and pouring the solution into dilute ammonia and filtering while still hot so as to avoid separation of ammonium picrate. The washed precipitate was suspended in dilute ammonia and shaken with ether. It was an amorphous, colourless solid, and could not be obtained crystalline. The ethereal solution had a green fluorescence.

Mitragynine distils unchanged at 230—240°/5 mm., the distillate forming white, amorphous crusts, m. p. 102—106°, yielding a picrate identical with that described above. Various salts were prepared by dissolving the alkaloid in ether and adding an ethereal solution of an acid. The salts with mineral acids have a great tendency to gelatinise; the hydrochloride was crystallised by careful addition of dry ether to its solution in 95 per cent. alcohol; it formed rhomb-shaped leaflets, m. p. 243°. The oxalate and tartrate were likewise unsatisfactory, but the acetate, mono-, and trichloro-acetates were obtained pure more easily.

The *acetate* was prepared by dissolving the base (recovered from the picrate) in ether and adding glacial acetic acid until a permanent precipitate was just formed. In a few hours the acetate separated (3·7 grams from 6 grams of pure picrate). Recrystallised from glacial acetic acid and ether, it formed slender, silky needles, m. p. 142°.

The *trichloroacetate* is, after the picrate, the salt most easily obtained pure of those investigated. It forms needles from acetone and ether, m. p. 157° (Found: Cl=19·35. $C_{22}H_{31}O_5N,CCl_3{\cdot}CO_2H$ requires Cl=19·25 per cent.).

Mitragynine contains three methoxy-groups, but no *N*-methyl group (Found, for base regenerated from pure picrate: MeO=21·8; 3MeO requires 23·9 per cent.; found, for acetate: MeO=17·8, 18·8; 3MeO requires 20·7 per cent. No more silver iodide was obtained at 340° by Herzig and Meyer's method). The product of the action of hydriodic acid and of hydrobromic acid was insoluble in most organic solvents, including pyridine and nitrobenzene, and decomposed at 380°

Action of Alkali on Mitragynine Acetate.

One gram of the acetate was boiled under reflux on the water-bath with 20 c.c. of alcoholic 2*N*-sodium ethoxide. The substance gradually dissolved. After three hours, the solution was cooled and neutralised with the calculated quantity of alcoholic hydrogen chloride. The sodium chloride which separated was filtered off, and the filtrate and alcoholic washings were concentrated to small bulk. The residue consisted of an amphoteric substance insoluble in ether, soluble in ammonia and in acid, and of a substance which dissolved in ether. The latter furnished a cream-coloured sublimate at 250°/2 mm., which gave an intense violet coloration when boiled with vanillin and hydrochloric acid, indicating the presence of an indole derivative. The amphoteric substance was washed free from alcohol by ether and dried in a vacuum. This substance contained one methoxy-group, so that two such groups had been eliminated by the alkaline hydrolysis (Found : $MeO=8{\cdot}3$. $C_{19}H_{24}O_4N[OMe]$ requires $MeO=8{\cdot}6$ per cent.). The product formed by hydrolysis with sodium ethoxide is therefore a dicarboxylic acid of the formula $C_{17}H_{22}N(OMe)(CO_2H)_2$ (assuming that the alkyl groups eliminated are methyl groups). The substance was amorphous, readily soluble in alcohol, but not in ether, and melted at 280°. It yielded no crystalline derivatives; in particular, the picrate, soluble in hot water, separated in a gelatinous condition on cooling. With a view to eliminate the carboxyl groups, 0·5 gram of the product of hydrolysis with sodium ethoxide was mixed with 2 grams of calcium oxide and heated in a metal-bath at 2 mm. pressure. About 0·2 gram of a glassy distillate was obtained, which dissolved in ether to a yellow solution, leaving on evaporation a viscous, green oil, no longer entirely soluble in ether. This base gave an amorphous hydrochloride and a red picrate, which was obtained crystalline from methyl alcohol in small quantity and melted fairly sharply at 218°. In subsequent experiments the yield of the red picrate could not be improved, and sometimes none was obtained. There is reason to believe that mitragynine is an indole derivative, or at least undergoes decomposition with the formation of such a substance. Apart from the coloration of the decomposition product referred to above, with vanillin and hydrochloric acid, and the formation of a red picrate, this is suggested by the fact that the acid resulting by hydrolysis of mitragynine gives the pinewood reaction on heating with soda-lime, and particularly on heating with zinc dust. Mitragynine itself, on boiling with vanillin and hydrochloric acid, gives a purple colour, and when concentrated sulphuric acid is poured under a solution of mitragynine containing glyoxylic acid, the sulphuric acid is coloured blue, reminiscent of the Adamkiewicz reaction for tryptophan.

Mitraversine, $C_{22}H_{26}O_4N_2$(?), *from* M. diversifolia.

One kilo. of leaves was percolated with 20 litres of 92 per cent. alcohol; after evaporation of the alcohol, the residue was dissolved in the minimum quantity of glacial acetic acid, and the solution poured into water. After filtration, the filtrate was made alkaline with ammonia, and extracted with ether. The ether (4 litres) was extracted twenty times with 10 per cent. acetic acid, the extracts, when made alkaline, giving a flocculent precipitate, which crystallised from methyl alcohol in a total yield of 0·27 per cent. of the weight of the leaves employed.

Mitraversine melts at 237°, is slightly soluble in boiling water and readily soluble in dilute sodium hydroxide solution and in dilute acids (Found: C=68·4; H=7·0; N=7·6. $C_{22}H_{26}O_4N_2$ requires C=69·1; H=6·8; N=7·3 per cent.). The molecular weight was determined by Barger's microscopic method (0·1526 in 5 c.c. of pyridine=0·0093 molar; M=328. $C_{22}H_{26}O_4N_2$ requires M=382). Mitraversine contains two methoxy-groups (Found: MeO=14·6. $C_{20}H_{20}O_2N_2[OMe]_2$ requires MeO=16·2 per cent.). The *hydrochloride* forms rhomb-shaped leaflets melting at 208—210° (Found: Cl=7·7. $C_{22}H_{26}O_4N_2$,HCl requires Cl=8·5 per cent.). Owing to the small amount of material available, the formula could not be settled definitely.

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